

REMARKS

In the Office Action of September 5, 2002, the Examiner objected to the specification for not including an Abstract. As the present application is the National Phase of a PCT application, the Abstract is found on the cover page of the application. With the present amendment the abstract is entered as new page 35 of the Specification.

Claims 1, 2, 4-6, 9 and 10 stand rejected under 35 U.S.C. § 1.12, second paragraph for being indefinite. The Examiner noted the double use of "D" in claim 1, and has rejected 2, 5, 6, 9 and 10 for being dependant on claim 1. In addition, claims 4 and 5 are said to lack antecedent basis because they recite the limitation of "(1-6 C) alkyl ester thereof," which is not recited in claim 1.

With the present amendments "D" as part of the formula, and printed in bold, is now replaced by "W." With this amendment to the specification and claims, any confusion between the "D" substituent and the common usage of "D" to denote right hand configuration is now avoided. In addition, claim 1 is now amended to include "glutanyl or a (C₁-C₆) alkyl ester thereof." Support for this amendment is found in the specification on page 4, lines 5 and 6 and in Example 8. It is also inherently supported by claims 4 and 5 as originally filed.

Claim 9 stands rejected under 35 U.S.C. § 1.12, first paragraph for lack of enablement.


Although Applicant's believe the Specification and the knowledge in the art of the skilled practitioner render a prodrug

Attorney Docket Number O 98411 US

as defined in the Specification to be enabled, claim 9 is canceled without prejudice in order to advance the prosecution of this application.

It is believed that with the present amendments claims 1-6 and 10 are in condition for allowance. Favorable action is solicited. Should it be believed that a conference would be helpful in advancing the prosecution of the application, the Examiner is invited to telephone Applicants' attorney at the number below.

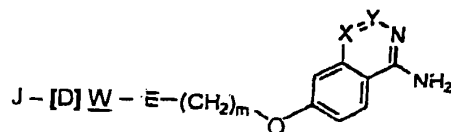
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IN THE CLAIMS (Marked Version)

1. (Twice Amended) A serine protease inhibitor having the formula (I),



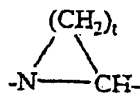
in which

J is H, R^1 , $R^1-O-C(O)-$, $R^1-C(O)-$, R^1-SO_2- , $R^3OOC-(CHR^2)_p-$, $(R^{2a}, R^{2b})N-CO-(CHR^2)_p-$ or $Het-CO-(CHR^2)_p-$;

[D]W is an amino-acid of the formula $-NH-CHR^1-C(O)-$, $-NR^4-CH((CH_2)_qC(O)OR^1)-C(O)-$, $-NR^4-CH((CH_2)_qC(O)N(R^{2a}, R^{2b}))-C(O)-$, $-NR^4-CH((CH_2)_qC(O)Het)-C(O)-$, D-1-Tiq, D-3-Tiq, D-Atc, Aic, D-1-Piq [or], D-3

Piq, glutanyl or a (C_1-C_6) alkylester thereof;

E is $-NR^2-CH_2-$ or the fragment



, which is unsubstituted or substituted with (1-6C)alkyl, (1-6C)alkoxy or benzyloxy;

R^1 is selected from (1-12C)alkyl,

(2-12C)alkenyl, (2-12C)alkynyl, (3-12C)cycloalkyl and (3-12C)cycloalkyl(1-6C)alkylene, which groups are unsubstituted or substituted with (3-12C)cycloalkyl, (1-6C)alkoxy, oxo, OH, CF_3 or halogen, and from

(6-14C)aryl, (7-15C)aralkyl, (8-16C)aralkenyl and (14-20C)(bisary)alkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl,

(3-12C)cycloalkyl, (1-6C)alkoxy, OH, CF_3 or halogen;

R^2 , R^{2a} and R^{2b} are each independently selected from

H, (1-8C)alkyl, (3-8C)alkenyl, (3-8C)alkynyl,

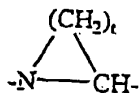
(3-8C)cycloalkyl and (3-6C)cycloalkyl(1-4C)alkylene, which are unsubstituted or substituted with (3-6C)cycloalkyl, (1-6C)alkoxy, CF_3 or halogen, and from (6-14C)aryl and (7-15C)aralkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF_3 or halogen;
 R^3 is the same as R^2 or is Het-(1-6C)alkyl;
 R^4 is H or (1-3C)alkyl;
X and Y are CH or N, with the proviso that they are not both N;
Het is a 4-, 5- or 6-membered heterocycle containing one or more heteroatoms selected from O, N and S;
m is 1 or 2;
p is 1, 2 or 3;
q is 1, 2 or 3;
t is 2, 3 or 4;
or a pharmaceutically acceptable addition salt or solvate thereof.

3. (Twice Amended) The serine protease inhibitor according to claim 2, wherein

J is H, $\text{R}^1 \text{R}^1\text{-SO}_2\text{-}$, $\text{R}^3\text{OOC-(CHR}^2\text{)}_p\text{-}$,
 $(\text{R}^{2a}, \text{R}^{2b})\text{N-CO-(CHR}^2\text{)}_p\text{-}$ or $\text{Het-CO(CHR}^2\text{)}_p\text{-}$;

$[\text{D}]\underline{\text{W}}$ is an amino-acid of the formula $\text{-NH-CHR}^1\text{-C(O)-}$,
 $\text{-NR}^4\text{-CH((CH}_2\text{)}_q\text{C(O)OR}^1\text{)-C(O)-}$,
 $\text{-NR}^4\text{-CH((CH}_2\text{)}_q\text{C(O)N(R}^{2a}, \text{R}^{2b})\text{)-C(O)-}$,

E is $\text{-N(3-6C)cycloalkyl-CH}_2\text{-}$ or the fragment



, which is unsubstituted or substituted with (1-6C)alkyl or 1-6C)alkoxy;

R^1 is selected from (1-12C)alkyl, (3-12C)cycloalkyl and

(3-12C)cycloalkyl(1-6C)alkylene, which groups are unsubstituted or substituted with (3-12C)cycloalkyl, (1-6C)alkoxy or oxo, and from (6-14C)aryl, (7-15C)aralkyl and (14-20C)(bisaryl)alkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-12C)cycloalkyl, (1-6C)alkoxy, OH, CF₃ or halogen;

R² is H;

R^{2a} and R^{2b} are each independently selected from H, (1-8C)alkyl, (3-8C)cycloalkyl and (3-6C)cycloalkyl(1-4C)alkylene, which are unsubstituted or substituted with (3-6C)cycloalkyl or (1-6C)alkoxy and from (6-14C)aryl and (7-15C)aralkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF₃ or halogen;

R³ is selected from H, (1-8C)alkyl, (3-8C)cycloalkyl and (3-6C)cycloalkyl(1-4C)alkylene, which are unsubstituted or substituted with (3-6C)cycloalkyl or (1-6C)alkoxy, and from (7-15C)aralkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF₃ or halogen and from Het-(1-6C)alkyl;

p is 1;

q is 2;

t is 3 or 4.

4. (Twice Amended) The serine protease inhibitor according to claim 3, wherein

[D]W is an amino-acid of the formula -NH-CHR¹-C(O)- or glutamyl or an (1-6C)alkylester thereof;

R¹ is selected from (3-12C)cycloalkyl and (3-12C)cycloalkyl(1-6C)alkylene, which groups are unsubstituted or substituted with (3-12C)cycloalkyl

or (1-6C)alkoxy, and from (6-14C)aryl, (7-15C)aralkyl and (14-20C)(bisary)alkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-12C)cycloalkyl, (1-6C)alkoxy or halogen; and

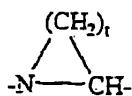
R³ is selected from (1-8C)alkyl and (3-8C)cycloalkyl, which are unsubstituted or substituted with (3-6C)cycloalkyl or (1-6C)alkoxy, and from (7-15C)aralkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF₃ or halogen and from Het-(1-6C)alkyl.

5. (Twice Amended) The serine protease inhibitor according to claim 4, wherein

J is -CH₂COO(1-6C)alkyl, (3-8C)cycloalkyl, -SO₂-10-camphor, -CH₂CONHphenyl or -CH₂CONH(3-8C)cycloalkyl;

[D]W is D-cyclohexylalaninyl, D-phenylalaninyl, D-diphenylalaninyl or glutamyl, or an (1-6C)alkylester thereof; and

E is the fragment



, wherein t is 3 or 4.

SERINE PROTEASE INHIBITOR

(Marked Version to show Changes Made)

The invention relates to a serine protease inhibitor comprising an ether bonded arginine replacement, a pharmaceutical composition containing the same, as well as
 5 the use of said serine protease inhibitor for the manufacture of a medicament.

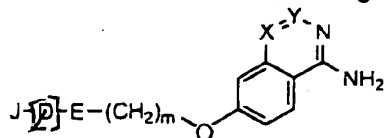
Serine proteases are enzymes which play an important role in the blood coagulation cascade. Apart from thrombin and factor Xa, other examples of this group of proteases comprise the factors VIIa, IXa, XIa, XIIa, and protein C.

10 Thrombin is the final serine protease enzyme in the coagulation cascade. The prime function of thrombin is the cleavage of fibrinogen to generate fibrin monomers, which are cross-linked to form an insoluble gel. In addition, thrombin regulates its own production by activation of factors V and VIII earlier in the cascade. It also has important actions at cellular level, where it acts on specific receptors to cause platelet
 15 aggregation, endothelial cell activation and fibroblast proliferation. Thus thrombin has a central regulatory role in haemostasis and thrombus formation. Since inhibitors of thrombin may have a wide range of therapeutic applications, there is a continuous effort to find new serine protease inhibitors. The difficulty in this endeavour is to find a compound in which the properties of therapeutic safety, selectivity, potency and
 20 synthetic accessibility are combined. In particular the bioavailability with the oral route of administration can be problematic for selective thrombin inhibitors.

In WO 97/16444 thrombin inhibitors are described with modifications of the tripeptide sequence phenylalanyl-prolyl-arginine, in which a carboxyl group is present at the amino terminal and arginine is replaced by a basic (aminoiminomethyl)phenyl
 25 or a basic (aminoiminomethyl)pyridinyl group linked to a prolyl analogue by an ether bond.

It is the object of this invention to provide new chemically accessible serine protease inhibitors with a favourable pharmacological and toxicological profile with sufficient
 30 potency for therapeutic use.

It has been found that this object can be met with a serine protease inhibitor, and in particular a thrombin inhibitor, having the formula (I).



Formula (I)

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in which



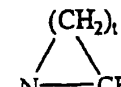
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J is H, R¹, R¹-O-C(O)-, R¹-C(O)-, R¹-SO₂-, R³OOC-(CHR²)_p-, (R^{2a}, R^{2b})N-CO-(CHR²)_p- or Het-CO-(CHR²)_p-;

[D] W¹ ← [D] is an amino-acid of the formula -NH-CHR¹-C(O)-, -NR⁴-CH[(CH₂)_qC(O)OR¹]-C(O)-, -NR⁴-CH[(CH₂)_qC(O)N(R^{2a}, R^{2b})]-C(O)-, -NR⁴-CH[(CH₂)_qC(O)Het]-C(O)-, D-1-Tiq, D-3-Tiq, D-Atc, Aic, D-1-Piq or D-3-Piq;

5 3-Tiq, D-Atc, Aic, D-1-Piq or D-3-Piq;

E is -NR²-CH₂- or the fragment



, optionally substituted with (1-6C)alkyl, (1-6C)alkoxy or benzyloxy;

10 R¹ is selected from (1-12C)alkyl, (2-12C)alkenyl, (2-12C)alkynyl, (3-12C)cycloalkyl and (3-12C)cycloalkyl(1-6C)alkylene, which groups may optionally be substituted with (3-12C)cycloalkyl, (1-6C)alkoxy, oxo, OH, CF₃ or halogen, and from (6-14C)aryl, (7-15C)aralkyl, (8-16C)aralkenyl and (14-20C)(bisaryl)alkyl, whereby the aryl groups may optionally be substituted with (1-6C)alkyl, (3-12C)cycloalkyl, (1-6C)alkoxy, OH, CF₃ or halogen;

15 R², R^{2a} and R^{2b} are each independently selected from H, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (3-8C)cycloalkyl and (3-6C)cycloalkyl(1-4C)alkylene, which can each be optionally substituted with (3-6C)cycloalkyl, (1-6C)alkoxy, CF₃ or halogen, and from (6-14C)aryl and (7-15C)aralkyl whereby the aryl groups may optionally be substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF₃ or halogen;

R³ is as defined for R² or Het-(1-6C)alkyl;

20 R⁴ is H or (1-3C)alkyl;

X and Y are CH or N with the proviso that they are not both N;

Het is a 4-, 5- or 6-membered heterocycle containing one or more heteroatoms selected from O, N and S;

m is 1 or 2;

25 p is 1, 2 or 3;

q is 1, 2 or 3;

t is 2, 3 or 4;

and prodrugs thereof;

and pharmaceutically acceptable addition salts and/or solvates thereof.

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In particular, the compounds of the invention may possess improved bioavailability after oral administration.

In preferred embodiments of this invention compounds have formula (I)

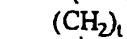
35 in which

J is H, R¹, R¹-SO₂-, R³OOC-(CHR²)_p-, (R^{2a}, R^{2b})N-CO-(CHR²)_p- or Het-CO-(CHR²)_p-; more preferred is (3-12C)cycloalkyl optionally substituted with (1-6C)alkoxy; or

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[D] ← [D] is an amino-acid of the formula $\text{-NH-CHR}^1\text{-C(O)-}$, $\text{-NR}^4\text{-CH}[(\text{CH}_2)_q\text{C(O)OR}^1]\text{-C(O)-}$, $\text{-NR}^4\text{-CH}[(\text{CH}_2)_q\text{C(O)N(R}^{2a}, \text{R}^{2b})]\text{-C(O)-}$, $\text{-NR}^4\text{-CH}[(\text{CH}_2)_q\text{C(O)Het}]\text{-C(O)-}$; more preferred are an amino acid of the formula $\text{-NH-CHR}^1\text{-C(O)-}$ or an L-amino acid of the formula $\text{-NR}^4\text{-CH}[(\text{CH}_2)_2\text{C(O)N(R}^{2a}, \text{R}^{2b})]\text{-C(O)-}$; or

5 E is $\text{-N(3-6C)cycloalkyl-CH}_2\text{-}$ or the fragment



optionally substituted with (1-6C)alkyl, (1-6C)alkoxy or benzyloxy; more preferred is without substitution; or

R¹ is selected from (1-12C)alkyl, (3-12C)cycloalkyl and

10 (3-12C)cycloalkyl(1-6C)alkylene, which groups may optionally be substituted with (3-12C)cycloalkyl, (1-6C)alkoxy, or oxo and from (6-14C)aryl, (7-15C)aralkyl and (14-20C)(bisaryl)alkyl, whereby the aryl groups may optionally be substituted with (1-6C)alkyl, (3-12C)cycloalkyl, (1-6C)alkoxy, OH, CF₃ or halogen; more preferred is a selection from (3-12C)cycloalkyl and (3-12C)cycloalkyl(1-6C)alkylene, which groups may optionally be substituted with (3-12C)cycloalkyl or (1-6C)alkoxy, and

15 from (6-14C)aryl, (7-15C)aralkyl and (14-20C)(bisaryl)alkyl, whereby the aryl groups may optionally be substituted with (1-6C)alkyl, (3-12C)cycloalkyl, (1-6C)alkoxy or halogen; or

R² is H; or

20 R^{2a} and R^{2b} are each independently selected from H, (1-8C)alkyl, (3-8C)cycloalkyl and (3-6C)cycloalkyl(1-4C)alkylene, which can each be optionally substituted with (3-6C)cycloalkyl or (1-6C)alkoxy, and from (6-14C)aryl and (7-15C)aralkyl whereby the aryl groups may optionally be substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF₃ or halogen; or

R³ is selected from H, (1-8C)alkyl, (3-8C)cycloalkyl and

25 (3-6C)cycloalkyl(1-4C)alkylene, which can each be optionally substituted with (3-6C)cycloalkyl or (1-6C)alkoxy, and from (7-15C)aralkyl whereby the aryl groups may optionally be substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF₃ or halogen and from Het-(1-6C)alkyl; more preferred is a selection from (1-8C)alkyl and (3-8C)cycloalkyl, which can each be optionally substituted with (3-6C)cycloalkyl or (1-6C)alkoxy, and from (7-15C)aralkyl whereby the aryl groups may optionally be substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF₃ or halogen and from Het-(1-6C)alkyl; or

30

R⁴ is H or (1-3C)alkyl; or

X and Y are CH; or

35 Het is a 4-, 5- or 6-membered heterocycle containing one or more heteroatoms selected from O, N and S; or

m is 2; or

4

p is 1; or

q is 2; or

t is 3 or 4; more preferred is 4.

[D] W

- 5 In further preferred embodiments [D] is an amino-acid of the formula -NH-CHR¹-C(O)- or glutamyl [or an (1-6C)alkylester thereof];

R¹ is selected from (3-12C)cycloalkyl and (3-12C)cycloalkyl(1-6C)alkylene, which groups may optionally be substituted with (3-12C)cycloalkyl or (1-6C)alkoxy, and from (6-14C)aryl, (7-15C)aralkyl and (14-20C)(bisaryl)alkyl, whereby the aryl groups may

- 10 optionally be substituted with (1-6C)alkyl, (3-12C)cycloalkyl, (1-6C)alkoxy or halogen; and R³ is selected from (1-8C)alkyl and (3-8C)cycloalkyl, which can each be optionally substituted with (3-6C)cycloalkyl or (1-6C)alkoxy, and from (7-15C)aralkyl whereby the aryl groups may optionally be substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF₃ or halogen and from Het-(1-6C)alkyl.

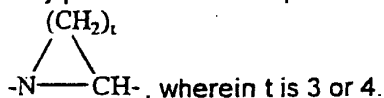
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Particularly preferred are compounds wherein J is -CH₂COO(1-6C)alkyl, (3-8C)cycloalkyl, -SO₂-10-camphor, -CH₂CONHphenyl or -CH₂CONH(3-8C)cycloalkyl.

Other highly preferred compounds are those wherein [D] is D-cyclohexylalaninyl, D-phenylalaninyl, D-diphenylalaninyl or glutamyl [or an (1-6C)alkylester thereof]. Also

[D] W

- 20 particularly preferred are compounds wherein E is the fragment



Herein the terms have the following meaning:

- (1-12C)alkyl, (1-8C)alkyl, (1-6C)alkyl, (1-3C)alkyl means a branched or unbranched
 25 alkyl group having 1-12, 1-8, 1-6 and 1-3 carbon atoms, respectively, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, hexyl, octyl and the like.
 (2-12C)alkenyl and (2-8C)alkenyl means a branched or unbranched alkenyl group having 2-12, and 2-8 carbon atoms, respectively, such as ethenyl, 2-butenyl, etc..
 (2-12C)alkynyl and (2-8C)alkynyl means a branched or unbranched alkynyl group
 30 having 2-12 and 2-8 carbon atoms, respectively, such as ethynyl, propynyl, etc..
 (1-6C)alkoxy means an alkoxy group having 1-6 carbon atoms, the alkyl moiety having the meaning as previously defined.
 (3-12C)cycloalkyl, (3-8C)cycloalkyl, (3-6C)cycloalkyl means a mono- or bicycloalkyl group having 3-12, 3-8 and 3-6 carbon atoms, respectively, like cyclopropyl,
 35 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclo-octyl, etc..

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production and handling. Binders are for example cellulose, starches, polyvinylpyrrolidone, and the like.

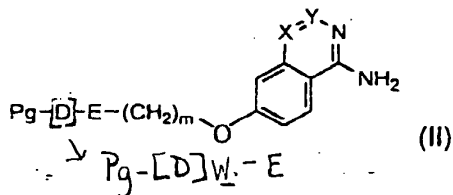
- 5 A suitable lubricant with which the active agent of the invention can be administered is, for example, magnesium stearate.

- 10 Surfactants are agents facilitating the contact and migration of compounds in different physical environments such as hydrophilic and hydrophobic environments. Many surfactants are known in the art of making pharmaceutical compositions as for example described in chapter 19 of Remington's Pharmaceutical Sciences (18th edition Editor A.R. Gennaro; Mack Publishing Comp; Easton, Pennsylvania). Surfactants that can be used during the process of preparing the pharmaceutical formulation are, for example, polyethylene glycol (PEG), and the like.

- 15 The compounds may also be used with implantable pharmaceutical devices such as those described in US Patent 4,767,628, the contents of which are incorporated by this reference. Then the device will contain sufficient amounts of compound to slowly release the compound (e.g. for more than a month).

- 20 Compounds of formula (I) may be prepared from a compound of formula (II), or derivatives thereof wherein the amino group at the aromatic group (arylamino) is protected as urethane such as Alloc or amide such as benzoyl, wherein $[D]$ E, X, Y and m have the previously defined meaning and Pg is an N-protecting group $[D]$ W (preferably urethane such as Boc).

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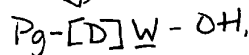
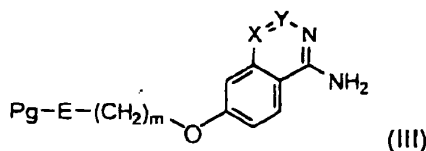


- The term N-protecting group as used in this document means a group commonly used in peptide chemistry for the protection of an α -amino group, like the allyloxycarbonyl (Alloc) group, the *tert*-butyloxycarbonyl (Boc) group, the benzyloxycarbonyl (Z) group, the 9-fluorenylmethyloxycarbonyl (Fmoc) group or the phthaloyl (Phth) group. Removal of the protecting groups can take place in different ways, depending on the nature of those protecting groups. An overview of amino protecting groups and methods for their removal is given in the above mentioned The
- 30 Peptides, Analysis, Synthesis, Biology, Vol 3. and in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, 1991, John Wiley & Sons, Inc.
- 35

Removal of the N-protecting group Pg and optional modification(s) of the deprotected amine group using methods known in the field such as peptide coupling, alkylation or reductive amination give compounds of formula (I).

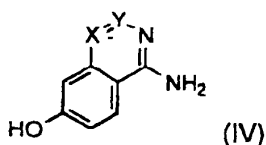
- 5 Compounds of formula (II) can be prepared from a compound of formula (III), or derivatives thereof wherein the arylamino is protected as urethane such as Alloc or amide such as benzoyl, wherein E, X, Y, m and Pg have the previously defined meanings. Removal of the N-protecting group Pg in compounds of formula (III) and peptide coupling with compounds of formula $\text{Pg}-[\text{D}]\text{OH}$, in which [D] and Pg have the previously defined meaning, yields compounds of formula (II).

10



- 15 Alternatively, compounds of formula (I) can be prepared directly from compounds of formula (III). Removal of the N-protecting group Pg in compounds of formula (III) and a peptide coupling with a compound of formula $\text{J}-[\text{D}]\text{OH}$, in which J and [D] have the previously defined meanings and may optionally contain a $\text{J}-[\text{D}]\text{W}-\text{OH}$ additional protecting group, afford compounds of formula (I).

- 20 Compounds of formulas (I), (II) and (III) are accessible from those of formula (IV) wherein X and Y have the previously defined meanings, or derivatives thereof wherein the arylamino is protected as urethane such as Alloc or amide such as benzoyl, by reaction with alcohols of formula $\text{J}-[\text{D}]\text{E}-(\text{CH}_2)_m-\text{OH}$, $\text{Pg}-[\text{D}]\text{E}-(\text{CH}_2)_m-\text{OH}$ or $\text{Pg}-\text{E}-(\text{CH}_2)_m-\text{OH}$, in which [D], E, J, m and Pg have the previously defined meanings and optionally containing a protecting group, under standard Mitsunobu conditions (tributylphosphine, dialkyl azodicarboxylate) (R.L. Elliot, H. Kopecka, D.E. Gunn, H.-N. Lin and D.S. Garvey, *Bioorg. Med. Chem. Lett.*, 6, 2283 (1996); K. Wisniewski, A.S. Koldziejczyk and B. Falkiewicz, *J. Pept. Sc.*, 4, 1 (1998)).



- 30 Alcohols of type formula $\text{Pg}-\text{E}-(\text{CH}_2)_m-\text{OH}$ in which $\text{E} = -\text{R}^3\text{NCH}_2-$ and $m = 2$ are accessible by conjugate addition of the corresponding amine R^3NH_2 to ethyl acrylate, reduction of the ester function with lithium aluminium hydride, and subsequent introduction of the N-protecting group Pg.